CASE REPORT

A PATIENT WITH PENICILLIN-RESISTANT VIRIDANS GROUP STREPTOCOCCAL ENDOCARDITIS AND UNUSUAL REACTIONS TO VANCOMYCIN

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Abstract. There is a paucity of data regarding the treatment of endocarditis caused by penicillin-resistant viridans group streptococci (PR-VGS). We report a 16-year-old girl who had native-valve endocarditis due to PR-VGS which was identified as *Streptococcus mitis*. She also had unusual reactions to vancomycin. Eighteen hours after initiation of 50 mg/kg/day vancomycin, she developed a maculopapular rash, then at 48 hours she developed an intermittent high fever and a progressive decrease in peripheral leukocytes and platelets. She developed hypotension on Day 8. Her serum C-reactive protein and procalcitonin levels were high. All reactions improved after vancomycin was discontinued and oral prednisolone was started. This unusual combination of reactions to vancomycin was likely caused by immune and non-immune mechanisms. Her endocarditis was successfully treated with cefotaxime 200 mg/kg/day for 4 weeks.

INTRODUCTION

Viridans group streptococci (VGS) are common etiologic agents in community-acquired native valve endocarditis. The American Heart Association defines penicillin-resistant VGS (PR-VGS) as endocarditis-causing VGS that has a penicillin MIC >0.5 µg/ml (Baddour *et al*, 2005). There is a paucity of data on the treatment of PR-VGS endocarditis (Levy *et al*, 2001; Baddour *et al*, 2005; Knoll *et al*, 2007; Fujitani *et al*, 2008). We present an adolescent who was treated with vancomycin for PR-VGS native-valve endocarditis. She had unusual reactions to vancomycin and her endocarditis was successfully treated with cefotaxime.

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CASE REPORT

A 16-year-old Thai girl had complex congenital cyanotic heart disease (ventricular septal defect, pulmonary atresia, and major aortopulmonary collateral arteries). She was hospitalized in March 2007 because of fever for 2 weeks. She had dental treatment, and received amoxicillin prophylaxis for endocarditis, 2 weeks before developing fever. An echocardiogram revealed echo-bright masses of 22 x 14 mm on the posterior mitral valve leaflet and 10 x 5 mm on the tricuspid valve. Both blood culture specimens yielded VGS strain that was identified as *Streptococcus*

mitis by use of conventional biochemical testing and the API-20-STREP system. The antibiotic disk diffusion test revealed the organism was not susceptible to penicillin, but was susceptible to chloramphenicol, tetracycline and vancomycin. The E-test (AB Biodisk) showed the organism was resistant to penicillin as defined by the American Heart Association for endocarditis (MIC 1.5 μg/ml), but susceptible to cefotaxime (MIC 1.0 μg/ml).

Penicillin G (400,000 IU/kg/day) and gentamicin (5 mg/kg/day) were initially administered. The fever abruptly disappeared and a repeat blood culture 24 hours later did not yield any bacteria. On the third day of hospitalization when the organism was found non-susceptible to penicillin, the antimicrobial drugs were changed to vancomycin (Vancomycin®, CJ Corp, Kyunggi-Do, Korea) 50 mg/kg/day divided in 4 doses given intravenously over 1 hour. About 18 hours later (Day 1), she developed a pruritic, non-urticarial maculopapular rash on her back and legs, which gradually spread to her face and arms over the following 24 hours. She partially responded to treatment with hydroxyzine hydrochloride. The vancomycin was changed to another preparation (Vancomycin Sandoz®, Sandoz) and was given intravenously over 2 hours together with chlorpheniramine pretreatment, but the rash persisted. At 48 hours of vancomycin therapy, she started having intermittent high fever without any detectable new infection or localizing inflammation. Mucosal lesions were absent. There was no respiratory distress or pulmonary wheezing. She had nausea and vomited once daily on Days 6 and 7 of vancomycin therapy. Viral exanthematous fever was suspected on the basis of the clinical findings and complete blood count tests. On Day 8, she developed hypotension without any evidence of extraordinary loss of body fluid. Her blood pressure normalized by 2 hours of rapid intravenous fluid resuscitation, prednisolone administration, and discontinuation of vancomycin for suspicion of vancomycin reaction. Dengue shock syndrome was also suspected but all the serologic tests for dengue infection were negative. A serum tryptase level, a marker for mast cell activation, was normal 30 minutes after detection of hypotension.

While the patient was receiving vancomycin, her leukocyte, neutrophil, and platelet counts gradually decreased. Platelet HLA-antibody was not detectable, but vancomycin-dependent antiplatelet antibody was not tested. Her serum hepatic transaminases and creatinine were normal and a urinalysis was normal. Her C-reactive protein (CRP) level, which was high (34.5 mg/l) before treatment, decreased to normal (7.0 mg/l) on Day 6 of vancomycin therapy. Her serum CRP and procalcitonin (PCT) levels were high (23.5 mg/l and 1.889 μg/l) when the patient developed hypotension (Day 8) and continued to increase on the following day.

On Day 8, vancomycin was changed to cefotaxime 200 mg/kg/day in 4 divided doses and oral prednisolone 0.5 mg/kg/day was given. Her fever abruptly disappeared. The skin rash gradually decreased and completely disappeared 6 days later. The peripheral blood cell counts were at their nadir (leukocytes 3,190 cells/μl, neutrophils 2,200 cells/μl, platelets 123 x 10^3 cells/μl), and CRP and PCT levels peaked (26.9 mg/dl and 3.898 μg/l) one day after vancomycin was discontinued, and all returned to their normal values in 3-5 days. Prednisolone was tapered over 5 days. Cefotaxime was administered for an additional 20 days to complete the 4-week treatment. An echocardiogram 5 months after completion of antimicrobial treatment did not reveal any vegetations. She remained well 12 months later.

DISCUSSION

Case reports on the treatment of PR-VGS endocarditis are rare. This patient had PR-VGS

native valve endocarditis and an unusual vancomycin reaction. She was successfully treated with single-drug therapy, namely, vancomycin followed by cefotaxime.

The American Heart Association's scientific statement in 2005 recommended that a patient with PR-VGS endocarditis should be treated with a regimen recommended for enterococcal endocarditis, which is a combination of high-dose penicillin G or ampicillin and gentamicin, or vancomycin with or without gentamicin (Baddour *et al*, 2005). Our patient had an adverse drug reaction to vancomycin; she made an uneventful recovery when the drug was changed to cefotaxime. There have been few reports on successful treatment of PR-VGS endocarditis with ceftriaxone with or without an aminoglycoside (Levy *et al*, 2001; Knoll *et al*, 2007; Fujitani *et al*, 2008), and ceftriaxone plus gentamicin was recently suggested to be added to the treatment recommendation (Fujitani *et al*, 2008). Cefotaxime has a similar antimicrobial spectrum to cefriaxone, but less information is available regarding cefotaxime treatment of PR-VGS endocarditis because of the ease of ceftriaxone administration. Our experience in this case suggests that cefotaxime is a potential alternative for patients with PR-VGS endocarditis, especially in whom ceftriaxone is not recommended.

The finding of progressive reactions to vancomycin as occurred in our patient has not been reported. After initiation of vancomycin, the patient developed a skin rash by 18 hours, an intermittent high fever by 48 hours, and decreasing peripheral leukocytes and platelet counts, then, hypotension developed on Day 8. The patient did not have other disease, and did not receive any other medicines besides vancomycin and an antihistamine. All abnormalities returned to normal soon after vancomycin was discontinued and oral prednisolone was given.

Adverse reactions to vancomycin are of 2 types: non-immunologic and immunologic reactions. "red man syndrome" is the most common reaction and is related to rapid infusion, and degranulation of mast cells and basophils resulting in histamine release. It typically consists of itching, an erythematous rash that involves the face, neck and upper part of the trunk; hypotension occurs less frequently (Murray and Nannini, 2005). Our patient had an early vancomycin-induced maculopapular rash which could be due to a non-immune drug reaction similar to "red man syndrome". Fever and rash are uncommon in patients receiving vancomycin (Murray and Nannini, 2005).

The fever, which occurred 48 hours after vancomycin exposure, could be due to an immune-mediated "drug fever" as previously described (Olaison *et al*, 1999). While drug fever and neutropenia are common after prolonged use of penicillin (Olaison *et al*, 1999), such reaction is rare with vancomycin (Smith and Taylor, 1999; Murray and Nannini, 2005). Vancomycin-induced leukopenia, neutropenia, or thrombocytopenia has been infrequently reported; it occurrs in most cases without a preceding fever or rash (Murphy *et al*, 1983; Hassaballa *et al* 2000; von Drygalski *et al* 2007). In one study of adult patients treated with home intravenous vancomycin therapy, neutropenia occurred in 14/114 (12%) cases and the mean (± SD) time from initiation of vancomycin to neutropenia was 26 ± 15 days (Murphy *et al*, 1983). One study reported the nadir platelet count, in 29 adults who had thrombocytopenia while receiving vancomycin, averaged 8 days (range, 1 to 27) after initiation of vancomycin; the detection of vancomycin-dependent platelet-antibody in the studied patients suggested an immunologic process (von Drygalski *et al,* 2007). Our patient had fever and decreasing leukocytes, neutrophils and platelets during vancomycin therapy, but vancomycin was discontinued before more serious leukopenia and thrombocytopenia developed.

In our patient hypotension occurred on Day 8 of vancomycin administration, 7 days after the onset of skin rash and 6 days after the onset of fever. Vancomycin-induced hypotension may occur from the anaphylactoid reaction "red man syndrome" or anaphylaxis (Murray and Nannini, 2005). There was a report of a patient with vancomycin-induced red man syndrome who developed vancomycin anaphylaxis (Hassaballa *et al,* 2000). The mechanisms of hypotension in our case were unclear. It probably did not involve degranulation of mast cells as a serum tryptase level was normal, but it is possible that later elevations of tryptase were missed. Increased CRP and PCT levels when hypotension developed suggest an inflammatory process.

This patient, who had native-valve endocarditis due to PR-VGS, had an unusual combination of reactions due to vancomycin which were likely caused by different immune and non-immune mechanisms. Cefotaxime is suggested as an alternative drug for the treatment of PR-VGS native-valve endocarditis.

REFERENCES

Baddour LM, Wilson WR, Bayer AS, *et al*. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation* 2005; 111: e394-434.

Fujitani S, Rowlinson MC, George WL. Penicillin G-resistant viridans group streptococcal endocarditis and interpretation of the American Heart Association's guidelines for the treatment of infective endocarditis. *Clin Infect Dis* 2008; 46: 1064-6.

Hassaballa H, Mallick N, Orlowski J. Vancomycin anaphylaxis in a patient with vancomycin-induced red man syndrome. *Am J Ther* 2000; 7: 319-20.

Knoll B, Tleyjeh IM, Steckelberg JM, Wilson WR, Baddour LM. Infective endocarditis due to penicillin-resistant viridans group streptococci. *Clin Infect Dis* 2007; 44: 1585-92.

Levy CS, Kogulan P, Gill VJ, Croxton MB, Kane JG, Lucey DR. Endocarditis caused by penicillin-resistant viridans streptococci: 2 cases and controversies in therapy. *Clin Infect Dis* 2001; 33: 577-9.

Murphy MF, Riordan T, Minchinton RM, *et al*. Demonstration of an immune-mediated mechanism of penicillin-induced neutropenia and thrombocytopenia. *Br J Haematol* 1983; 55: 155-60.

Murray BE, Nannini EC. Glycopeptides (vancomycin and teicoplanin), streptogramins (quinupristin-dalfopristin), and lipopeptides (daptomycin). In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice in infectious diseases. 6th ed. Philadelphia: Elsevier Churchill Livingstone, 2005: 421.

Olaison L, Belin L, Hogevik H, Alestig K. Incidence of beta-lactam-induced delayed hypersensitivity and neutropenia during treatment of infective endocarditis. *Arch Intern Med* 1999; 159: 607-15.

Smith PF, Taylor CT. Vancomycin-induced neutropenia associated with fever: similarities between two immune-mediated drug reactions. *Pharmacotherapy* 1999; 19: 240-4.

Von Drygalski A, Curtis BR, Bougie DW, *et al*. Vancomycin-induced immune thrombocytopenia. *N Engl J Med* 2007; 356: 904-10.